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 NEWS  8  OCT 28  KOREAPAT now available on STN
 NEWS  9  NOV 18  Current-awareness alerts, saved answer sets, and current
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                  and SOLIDSTATE reloads
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 NEWS 11  DEC 01  LISA now available on STN

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=> s mutate or mutation
L1 846166 MUTATE OR MUTATION

=> s nucleobase analog?
L2 158 NUCLEOBASE ANALOG?

=> s nucleoside analog?
L3 19903 NUCLEOSIDE ANALOG?

=> s l2 or l3
L4 20032 L2 OR L3

=> s l1 (a) rate
L5 14396 L1 (A) RATE

=> s l5 (s) l4
L6 27 L5 (S) L4

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 13 DUP REM L6 (14 DUPLICATES REMOVED)

=> d ibib abs kwic tot l7

L7 ANSWER 1 OF 13 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004283729 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15183340
TITLE: Nucleoside-analog resistance mutations in HIV-1 reverse transcriptase and their influence on polymerase fidelity and viral mutation rates.
AUTHOR: Rezende Lisa F; Prasad Vinayaka R
CORPORATE SOURCE: Department of Microbiology and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Golding Building 401, Bronx, NY 10461, USA.
CONTRACT NUMBER: R01-AI30861 (NIAID)
T32-GM07491 (NIGMS)
SOURCE: international journal of biochemistry & cell biology, (2004 Sep) 36 (9) 1716-34.
Journal code: 9508482. ISSN: 1357-2725.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040609
Last Updated on STN: 20040725
AB Nucleoside-analog inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) were the first drugs used against the virus. It is long known that monotherapy with these and other drugs leads to the rapid development of viral resistance and it is being increasingly appreciated that a significant percentage of individuals receiving highly active antiretroviral therapy (HAART) also develop resistance. Considering the fact that RT is responsible both for optimal rate of replication and an accurate copying of the viral genome, the consequence of drug-resistance mutations in RT to the biochemistry of this enzyme and to the biology of the virus are critically important. The biochemistry of HIV-1 reverse transcriptase variants harboring nucleoside-analog resistance mutations has been studied extensively. In this review, we describe a number of studies into the polymerase fidelity of **nucleoside-analog** resistant HIV-1 reverse transcriptase

as well as the **mutation rate** of HIV-1 harboring these mutations.
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AB . . . resistance mutations has been studied extensively. In this review, we describe a number of studies into the polymerase fidelity of **nucleoside-analog** resistant HIV-1 reverse transcriptase as well as the **mutation rate** of HIV-1 harboring these mutations.
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L7 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:376555 CAPLUS
DOCUMENT NUMBER: 138:379194
TITLE: Ribonucleoside analogs for inhibition of RNA viruses
INVENTOR(S): Loakes, David; Brown, Daniel; Balzarini, Jan; Moriyama, Kei; Negishi, Kazuo; Cameron, Craig; Arnold, Jamie; Castro, Christian; Korneeva, Victoria; Graci, Jason
PATENT ASSIGNEE(S): Medical Research Council, UK
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039450	A2	20030515	WO 2002-GB5031	20021107
WO 2003039450	A3	20030821		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003130226	A1	20030710	US 2002-207005	20020730
EP 1441744	A2	20040804	EP 2002-772630	20021107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:
GB 2001-26701 A 20011107
US 2002-207005 A 20020730
WO 2002-GB5031 W 20021107

OTHER SOURCE(S): MARPAT 138:379194

AB The invention discloses pharmaceutical compns. containing ribonucleoside analogs, in admixt. with a physiol. acceptable excipient diluent or carrier. The ribonucleoside analogs of the invention inhibit the replication and/or increase the mutation rate of an RNA virus. Preparation of analogs is described. The compds. may be used to treat viral infections in animals, including humans, and plants.

ST antiviral nucleoside analog replication inhibition; **mutation rate** RNA virus antiviral **nucleoside analog**; nucleoside analog prepn antiviral RNA virus

L7 ANSWER 3 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003295743 EMBASE
TITLE: Fidelity of hepatitis B virus polymerase.
AUTHOR: Park S.G.; Kim Y.; Park E.; Ryu H.M.; Jung G.
CORPORATE SOURCE: G. Jung, School of Biological Sciences, Seoul National University, Seoul, 151-742, Korea, Republic of.

drjung@snu.ac.kr
SOURCE: European Journal of Biochemistry, (2003) 270/14 (2929-2936).
Refs: 45
ISSN: 0014-2956 CODEN: EJBCAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although efficient vaccines are available, chronic hepatitis B (HBV) infection poses a major health problem worldwide, and prolonged treatment of chronically infected HBV patients with **nucleoside analogs** often results in drug-resistant HBV variants. Therefore, it is critical to evaluate the contribution of the HBV polymerase to mutations. FLAG-tagged wild-type (FPolE) and mutant (FPolE/D551A) HBV polymerases have been expressed in insect cells and purified. The purified FPolE showed DNA polymerase activity, but FPolE/D551A did not, implying that the activity was derived from FPolE. No 3' → 5' exonuclease activity was detected in FPolE. The fidelity of FPolE was investigated and compared with that of HIV-1 RT, which is highly errorprone. The fidelity of HBV polymerase seems to be achieved by increasing the K(m) for the dNTP being misinserted. The nucleotide misinsertion efficiency of FPolE and HIV-1 RT ranged from 3.59 x 10(-4) (C:T) to 1.51 x 10(-3) (G:T) and from 1.75 x 10(-4) (C:T) to 1.62 x 10(-3) (G:T), respectively, and the overall misinsertion efficiency of HIV-1 RT was just 1.04-fold higher than that of FPolE, implying that HBV polymerase is fairly error-prone. Though HBV genetic **mutation rate** in replication is thought to be between those in RNA and DNA viruses, our data shows that the rate of mutation by HBV polymerase is higher than the rate of genetic mutation in vivo. This may be a result from more overlapping HBV genes in the HBV genome than that of other retroviruses.

AB . . . chronic hepatitis B (HBV) infection poses a major health problem worldwide, and prolonged treatment of chronically infected HBV patients with **nucleoside analogs** often results in drug-resistant HBV variants. Therefore, it is critical to evaluate the contribution of the HBV polymerase to mutations.. . . HIV-1 RT was just 1.04-fold higher than that of FPolE, implying that HBV polymerase is fairly error-prone. Though HBV genetic **mutation rate** in replication is thought to be between those in RNA and DNA viruses, our data shows that the rate of. . .

L7 ANSWER 4 OF 13 EMBASE
on STN

ACCESSION NUMBER: 2004280691 EMBASE
TITLE: Prophylaxis and treatment of hepatitis B recurrence after liver transplantation in the antiviral era.
AUTHOR: Seehofer D.; Rayes N.; Neuhaus P.
CORPORATE SOURCE: Dr. D. Seehofer, Dept. of Gen.-Visceral/Transp. Surg., Charite Campus Virschow, Augustenburger P Latz 1, D-13353 Berlin, Germany. daniel.seehofer@charite.de
SOURCE: Expert Review of Anti-Infective Therapy, (2003) 1/2 (307-318).
Refs: 74
ISSN: 1478-7210 CODEN: ERATCK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
036 Health Policy, Economics and Management
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Redistribution of virions from extrahepatic reservoirs with resultant reinfection of the graft is a serious complication after liver transplantation for hepatitis B-related liver disease. Prophylaxis of hepatitis B virus recurrence is a major issue in these patients. With the introduction of passive immunoprophylaxis and the development of antiviral drugs, liver transplantation has evolved as an established therapy of hepatitis B-induced end-stage liver failure. However, even under indefinite monoprophylaxis, a significant percentage of patients develop reinfection due to a high **mutation rate** of the hepatitis B virus. Progress, especially in the field of antiviral therapy, has opened new strategies, including combination prophylaxis and therapy, which further improve outcome. On the other hand, the broad use of antiviral drugs brings about new problems such as resistance formation prior to liver transplantation. In addition, due to the high costs of hepatitis B immunoglobulin alternatives such as prophylaxis with **nucleoside analogs** or vaccination are increasingly being investigated.

AB . . . B-induced end-stage liver failure. However, even under indefinite monoprophylaxis, a significant percentage of patients develop reinfection due to a high **mutation rate** of the hepatitis B virus. Progress, especially in the field of antiviral therapy, has opened new strategies, including combination prophylaxis. . . prior to liver transplantation. In addition, due to the high costs of hepatitis B immunoglobulin alternatives such as prophylaxis with **nucleoside analogs** or vaccination are increasingly being investigated.

L7 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003228373 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12749753
TITLE: Stealth nucleosides: mode of action and potential use in the treatment of viral diseases.
AUTHOR: Daifuku Richard
CORPORATE SOURCE: Koronis Pharmaceuticals, 12277 134th Court NE, Suite 110, Redmond, WA 98052, USA.. rdaifuku@koronispharma.com
SOURCE: BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, (2003) 17 (3) 169-77. Ref: 45
Journal code: 9705305. ISSN: 1173-8804.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20030517
Last Updated on STN: 20040323
Entered Medline: 20040322

AB Riboviruses and retroviruses have been shown to spontaneously mutate at an extraordinarily high rate. While this genetic diversity allows viral subpopulations to escape conventional antivirals, it also has a cost. Indeed, this high mutation rate results in the synthesis of many defective virions. Stealth nucleosides are **nucleoside analogues** that are designed to increase the already high spontaneous **mutation rate** of viruses to the point where the virus cannot further replicate, a process known as "lethal mutagenesis". Rather than causing chain termination and attempting to immediately halt viral replication, as with conventional nucleoside reverse transcriptase inhibitors (NRTI), stealth nucleosides are incorporated into the viral genome during replication and, by mispairing, cause mutations to the viral genome. These mutations affect all viral proteins and cumulatively, over a number of replication cycles, are lethal to the virus. There are two distinct stealth nucleoside platforms: DNA stealth nucleosides and RNA stealth nucleosides. DNA stealth nucleosides are currently being screened for activity against HIV and may have activity against hepatitis B virus

and smallpox virus, with the clinical lead DNA stealth nucleoside demonstrating activity in the low nanomolar range. In addition, DNA stealth nucleosides have been shown to be able to effectively treat NRTI-resistant HIV strains in vitro, which is not surprising given that the two principal modes of resistance (low affinity of reverse transcriptase for a modified sugar or pyrophosphorolysis) should not be applicable to DNA stealth nucleosides. RNA stealth nucleosides are being developed for the treatment of ribovirus infections, and particularly hepatitis C virus infection. RNA stealth nucleosides are selected for their broad spectrum of antiviral activity, and current lead RNA stealth nucleosides have potency in the same range as ribavirin.

AB . . . also has a cost. Indeed, this high mutation rate results in the synthesis of many defective virions. Stealth nucleosides are **nucleoside analogues** that are designed to increase the already high spontaneous **mutation rate** of viruses to the point where the virus cannot further replicate, a process known as "lethal mutagenesis". Rather than causing. . .

L7 ANSWER 6 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002312093 EMBASE

TITLE: Substitutions of Phe(61) located in the vicinity of template 5'-overhang influence polymerase fidelity and nucleoside analog sensitivity of HIV-1 reverse transcriptase.

AUTHOR: Fisher T.S.; Prasad V.R.

CORPORATE SOURCE: V.R. Prasad, Dept. of Microbiology, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, United States. prasad@aecom.yu.edu

SOURCE: Journal of Biological Chemistry, (21 Jun 2002) 277/25 (22345-22352).
Refs: 46
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Human immunodeficiency virus type 1 reverse transcriptase (RT) is an error-prone DNA polymerase. Structural determinants of its fidelity are incompletely understood. RT/template primer contacts have been shown to influence its fidelity and sensitivity to **nucleoside analog** inhibitors. The Phe(61) residue, located within the β3 sheet of the finger subdomain, is highly conserved among retroviral RTs. The crystal structure of a ternary complex revealed that Phe(61) contacts the first and second bases of the 5'-template overhang. To determine whether such contacts influence the dNTP-binding pocket, we performed a limited vertical scanning mutagenesis (Phe → Ala, Leu, Trp, or Tyr) at Phe(61). The F61A mutant displayed the highest increase in fidelity, followed by the F61L and F61W variants, which had intermediate phenotypes. F61Y RT had a minimal effect. The increase in fidelity of the F61A mutant was corroborated by a 12-fold decrease in its forward **mutation rate.** The Phe(61) mutant RTs also displayed large reductions in sensitivity to 2',3'-dideoxythymidine triphosphate and 2',3'-dideoxy,2'3'-didehydrothymidine triphosphate. Mutants displaying the largest increase in fidelity (F61A and F61L) were also the most resistant. These results suggest that contacts between the finger subdomain of human immunodeficiency virus type 1 RT and the template 5'-overhang are important determinants of the geometry of the dNTP-binding pocket.

AB . . . determinants of its fidelity are incompletely understood. RT/template primer contacts have been shown to influence its fidelity and sensitivity to **nucleoside analog** inhibitors. The Phe(61) residue, located within the β3 sheet of the finger subdomain, is highly conserved among retroviral RTs. The. . . a minimal effect.

The increase in fidelity of the F61A mutant was corroborated by a 12-fold decrease in its forward **mutation rate.** The Phe(61) mutant RTs also displayed large reductions in sensitivity to 2',3'-dideoxythymidine triphosphate and 2',3'-dideoxy,2'3'-didehydrothymidine triphosphate. Mutants displaying the largest. . .

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ACCESSION NUMBER: 2001340622 EMBASE
TITLE: Ribavirin: Recent insights into antiviral mechanisms of action.
AUTHOR: Reyes G.R.
CORPORATE SOURCE: G.R. Reyes, Infect. Disease and Oncology, Schering-Plough Research Inst., 2015 Galloping Hill Road, Kenilworth, NJ 07033, United States. gregory.reyes@spcorp.com
SOURCE: Current Opinion in Drug Discovery and Development, (2001) 4/5 (651-656).
Refs: 34
ISSN: 1367-6733 CODEN: CODDFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Ribavirin, a **nucleoside analog**, used in combination with interferon-α (IFNα) results in a substantial improvement in the sustained virologic response in chronic hepatitis C. Identified antiviral mechanisms of action for ribavirin include: (i) inhibition of viral encoded polymerases; (ii) inhibition of genomic RNA capping; and (iii) inhibition of cellular encoded enzymes that control de novo synthesis of purine nucleosides. More recently, ribavirin has been shown to engender a bias toward helper T-cell (CD4+) type 1 (Th1) cytokine responses in models of immunity. Recent detailed analysis has also shown that ribavirin can be utilized and incorporated by the polio viral polymerase into genomic and antigenomic transcripts, and is capable of base pairing with either UMP (uridine monophosphate) or CMP (cytidine monophosphate). This results in ribavirin-mediated mutagenesis of the viral genome and has the potential to push the virus beyond tolerable set points in its **mutation rate**, leading to an overall reduced fitness of the viral population. Of the many mechanisms of action demonstrated for ribavirin, the current clinical trials of selective inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitors and immunomodulating agents in hepatitis may facilitate our understanding of what activity (if any) predominates when ribavirin is used in combination with IFNα.

AB Ribavirin, a **nucleoside analog**, used in combination with interferon-α (IFNα) results in a substantial improvement in the sustained virologic response in chronic hepatitis C.. . . ribavirin-mediated mutagenesis of the viral genome and has the potential to push the virus beyond tolerable set points in its **mutation rate**, leading to an overall reduced fitness of the viral population. Of the many mechanisms of action demonstrated for ribavirin, the. . .

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ACCESSION NUMBER: 2001037570 EMBASE
TITLE: Review: Mitochondrial medicine - Molecular pathology of defective oxidative phosphorylation.
AUTHOR: Fosslien E.
CORPORATE SOURCE: Dr. E. Fosslien, Department of Pathology (M/C 847), College

of Medicine, University of Illinois at Chicago, 1819 West Polk Street, Chicago, IL 60612, United States. efosslie@uic.edu
SOURCE: Annals of Clinical and Laboratory Science, (2001) 31/1 (25-67).
Refs: 322
ISSN: 0091-7370 CODEN: ACLSCP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Different tissues display distinct sensitivities to defective mitochondrial oxidative phosphorylation (OXPHOS). Tissues highly dependent on oxygen such as the cardiac muscle, skeletal and smooth muscle, the central and peripheral nervous system, the kidney, and the insulin-producing pancreatic β-cell are especially susceptible to defective OXPHOS. There is evidence that defective OXPHOS plays an important role in atherogenesis, in the pathogenesis of Alzheimer's disease, Parkinson's disease, diabetes, and aging. Defective OXPHOS may be caused by abnormal mitochondrial biosynthesis due to inherited or acquired mutations in the nuclear (n) or mitochondrial (mt) deoxyribonucleic acid (DNA). For instance, the presence of a mutation of the mtDNA in the pancreatic β-cell impairs adenosine triphosphate (ATP) generation and insulin synthesis. The nuclear genome controls mitochondrial biosynthesis, but mtDNA has a much higher **mutation rate** than nDNA
because it lacks histones and is exposed to the radical oxygen species (ROS) generated by the electron transport chain, and the mtDNA repair system is limited. Defective OXPHOS may be caused by insufficient fuel supply, by defective electron transport chain enzymes (Complexes I - IV), lack of the electron carrier coenzyme Q10, lack of oxygen due to ischemia or anemia, or excessive membrane leakage, resulting in insufficient mitochondrial inner membrane potential for ATP synthesis by the F(0)F(1)-ATPase. Human tissues can counteract OXPHOS defects by stimulating mitochondrial biosynthesis; however, above a certain threshold the lack of ATP causes cell death. Many agents affect OXPHOS. Several nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit or uncouple OXPHOS and induce the 'topical' phase of gastrointestinal ulcer formation. Uncoupled mitochondria reduce cell viability. The Helicobacter pylori induces uncoupling. The uncoupling that opens the membrane pores can activate apoptosis. Cholic acid in experimental atherogenic diets inhibits Complex IV, cocaine inhibits Complex I, the poliovirus inhibits Complex II, ceramide inhibits Complex III, azide, cyanide, chloroform, and methamphetamine inhibit Complex IV. Ethanol abuse and antiviral **nucleoside analogue** therapy inhibit mtDNA replication.
By contrast, melatonin stimulates Complexes I and IV and Gingko biloba stimulates Complexes I and III. Oral Q10 supplementation is effective in treating cardiomyopathies and in restoring plasma levels reduced by the statin type of cholesterol-lowering drugs.
AB . . . impairs adenosine triphosphate (ATP) generation and insulin synthesis. The nuclear genome controls mitochondrial biosynthesis, but mtDNA has a much higher **mutation rate** than nDNA
because it lacks histones and is exposed to the radical oxygen species (ROS) generated by the electron transport. . . poliovirus inhibits Complex II, ceramide inhibits Complex III, azide, cyanide, chloroform, and methamphetamine inhibit Complex IV. Ethanol abuse and antiviral **nucleoside analogue** therapy inhibit mtDNA replication.
By contrast, melatonin stimulates Complexes I and IV and Gingko biloba stimulates Complexes I and III.. . .

ACCESSION NUMBER: 2000472659 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833521
TITLE: Differential influence of **nucleoside analog**-resistance mutations K65R and L74V on the overall **mutation rate** and error specificity of human immunodeficiency virus type 1 reverse transcriptase.
AUTHOR: Shah F S; Curr K A; Hamburgh M E; Parniak M; Mitsuya H; Arnez J G; Prasad V R
CORPORATE SOURCE: Division of Pediatric Infectious Diseases, Children's Hospital at Montefiore, Bronx, New York 10467, USA.
CONTRACT NUMBER: AI40375 (NIAID)
T32-AI07501 (NIAID)
T32-GM07491 (NIGMS)
SOURCE: Journal of biological chemistry, (2000 Sep 1) 275 (35) 27037-44.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001003

AB Human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) variants with the K65R or L74V substitution display resistance to several nucleoside analogs. An in vitro dNTP exclusion assay revealed an increased fidelity for K65R RT compared with wild-type RT, but little change for L74V RT. When the forward mutation rates were measured via a gap-filling assay, the K65R variant displayed an 8-fold decrease in the overall mutation rate (1.0 x 10(-3) versus 8.6 x 10(-3) for wild-type HIV-1 RT), whereas the rate for the L74V variant was closer to that for wild-type RT (5.0 x 10(-3)). The increase in overall fidelity observed for K65R RT is the largest reported for any drug-resistant HIV-1 RT variant. Nucleotide sequence analysis of lacZalpha mutants generated by variant RTs indicated that K65R RT displays uniform reduction in most types of errors, whereas L74V RT does not. Modeling the substitutions into the x-ray structure of the ternary complex revealed that the major influence of Leu(74) in stabilizing the templating base is unaffected by Val substitution, whereas the K65R substitution appears to increase the stringency of dNTP binding. It is speculated that the increased fidelity of K65R RT is due to an altered interaction with the dNTP substrate.

TI Differential influence of **nucleoside analog**-resistance mutations K65R and L74V on the overall **mutation rate** and error specificity of human immunodeficiency virus type 1 reverse transcriptase.

L7 ANSWER 10 OF 13 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:142265 BIOSIS
DOCUMENT NUMBER: PREV200200142265
TITLE: Differential influence of **nucleoside analog** resistance mutations K65R and L74V on the overall **mutation rate** and error specificity of HIV-1 reverse transcriptase.
AUTHOR(S): Shah, F. S. [Reprint author]; Curr, K.; Hamburgh, M.; Parniak, M.; Mitsuya, H.; Prasad, V. R.
CORPORATE SOURCE: Div. Of Pediatric Infectious Diseases, Children's Hospital At Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA
SOURCE: Journal of Investigative Medicine, (March, 2000) Vol. 48, No. 2, pp. 221A. print.
Meeting Info.: Eastern Society for Pediatric Research. Eastern Society for Pediatric Research.

ISSN: 1081-5589.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002
TI Differential influence of **nucleoside analog** resistance mutations K65R and L74V on the overall **mutation rate** and error specificity of HIV-1 reverse transcriptase.

L7 ANSWER 11 OF 13 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999145577 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9990051
TITLE: Lethal mutagenesis of HIV with mutagenic nucleoside analogs.
AUTHOR: Loeb L A; Essigmann J M; Kazazi F; Zhang J; Rose K D; Mullins J I
CORPORATE SOURCE: Joseph Gottstein Memorial Cancer Research Laboratory, Department of Pathology, University of Washington, Seattle, WA 98195, USA.. laloeb@u.washington.edu
CONTRACT NUMBER: AI-42570 (NIAID)
R35-CA-39903 (NCI)
R35-CA52127 (NCI)
+
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 Feb 16) 96 (4) 1492-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990325
AB The human immunodeficiency virus (HIV) replicates its genome and mutates at exceptionally high rates. As a result, the virus is able to evade immunological and chemical antiviral agents. We tested the hypothesis that a further increase in the **mutation rate** by promutagenic **nucleoside analogs** would abolish viral replication. We evaluated deoxynucleoside analogs for lack of toxicity to human cells, incorporation by HIV reverse transcriptase, resistance to repair when incorporated into the DNA strand of an RNA.DNA hybrid, and mispairing at high frequency. Among the candidates tested, 5-hydroxydeoxycytidine (5-OH-dC) fulfilled these criteria. In seven of nine experiments, the presence of this analog resulted in the loss of viral replicative potential after 9-24 sequential passages of HIV in human CEM cells. In contrast, loss of viral replication was not observed in 28 control cultures passaged in the absence of the nucleoside analog, nor with other analogs tested. Sequence analysis of a portion of the HIV reverse transcriptase gene demonstrated a disproportionate increase in G --> A substitutions, mutations predicted to result from misincorporation of 5-OH-dC into the cDNA during reverse transcription. Thus, "lethal mutagenesis" driven by the class of deoxynucleoside analogs represented by 5-OH-dC could provide a new approach to treating HIV infections and, potentially, other viral infections.
AB . . . virus is able to evade immunological and chemical antiviral agents. We tested the hypothesis that a further increase in the **mutation rate** by promutagenic **nucleoside analogs** would abolish viral replication. We evaluated deoxynucleoside analogs for lack of toxicity to human cells, incorporation by HIV reverse transcriptase,. . .

L7 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 97296228 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9151812
TITLE: The antiretrovirus drug 3'-azido-3'-deoxythymidine increases the retrovirus mutation rate.
AUTHOR: Julias J G; Kim T; Arnold G; Pathak V K
CORPORATE SOURCE: Department of Biochemistry, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown 26506, USA.
CONTRACT NUMBER: CA58875 (NCI)
SOURCE: Journal of virology, (1997 Jun) 71 (6) 4254-63.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970609

AB It was previously observed that the **nucleoside analog** 5-azacytidine increased the spleen necrosis virus (SNV) **mutation rate** 13-fold in one cycle of retrovirus replication (V. K. Pathak and H. M. Temin, J. Virol. 66:3093-3100, 1992). Based on this observation, we hypothesized that nucleoside analogs used as antiviral drugs may also increase retrovirus mutation rates. We sought to determine if 3'-azido-3'-deoxythymidine (AZT), the primary treatment for human immunodeficiency virus type 1 (HIV-1) infection, increases the retrovirus mutation rate. Two assays were used to determine the effects of AZT on retrovirus mutation rates. The strategy of the first assay involved measuring the in vivo rate of inactivation of the lacZ gene in one replication cycle of SNV- and murine leukemia virus-based retroviral vectors. We observed 7- and 10-fold increases in the SNV mutant frequency following treatment of target cells with 0.1 and 0.5 microM AZT, respectively. The murine leukemia virus mutant frequency increased two- and threefold following treatment of target cells with 0.5 and 1.0 microM AZT, respectively. The second assay used an SNV-based shuttle vector containing the lacZ alpha gene. Proviruses were recovered as plasmids in Escherichia coli, and the rate of inactivation of lacZ alpha was measured. The results indicated that treatment of target cells increased the overall mutation rate two- to threefold. DNA sequence analysis of mutant proviruses indicated that AZT increased both the deletion and substitution rates. These results suggest that AZT treatment of HIV-1 infection may increase the degree of viral variation and alter virus evolution or pathogenesis.
AB It was previously observed that the **nucleoside analog** 5-azacytidine increased the spleen necrosis virus (SNV) **mutation rate** 13-fold in one cycle of retrovirus replication (V. K. Pathak and H. M. Temin, J. Virol. 66:3093-3100, 1992). Based on. . .

L7 ANSWER 13 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95183233 EMBASE
DOCUMENT NUMBER: 1995183233
TITLE: Combination antiretroviral therapy. Back to the future.
AUTHOR: Lange J.
CORPORATE SOURCE: Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, Meibergreef 9,1105 AZ Amsterdam, Netherlands
SOURCE: Drugs, (1995) 49/SUPPL. 1 (32-37).
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HIV causes chronic infection and is associated with persistent viral replication and a high viral **mutation rate.** It is an illusion to think that monotherapy with any antiretroviral agent will have a major and lasting impact on this disease. Monotherapy with antitubercular agents led to dramatic improvements in treatment, but the development of drug resistance meant that these improvements were of only short duration, and hence it was concluded that drugs should be combined. The response to the limited efficacy of **nucleoside analogue** monotherapy in HIV infection has in many instances been the stance that 'currently available antiretrovirals are no good; it is better not to treat'. In addition, regulatory insistence on clinical end-points has also hampered antiretroviral drug development. It is implied that antiretrovirals must be tested in populations with fairly advanced HIV infection, in whom the least success may be expected. The regulatory bind has also resulted in artificial and counterproductive treatment guidelines. Common sense and experience in infectious diseases dictate that treatment should hit hard and early. No study published thus far undermines the concept that early therapy is better than late therapy or that a tolerable combination of drugs with additive or synergistic anti-HIV activity is better than nucleoside monotherapy. Promising data have been generated in trials on combinations of zidovudine plus didanosine or zalcitabine; a combination of zidovudine and lamivudine (3TC) may be even more promising. However, with 2-drug combinations there still is suboptimal suppression of HIV virus load. In vitro findings indicate that most 3-drug combinations are more effective at suppressing virus production than 2-drug combinations, and a good number of antiretroviral agents that could have a place in triple-drug regimens are available. Thus, we should proceed expeditiously with the clinical testing of triple-drug combinations. This can only be done efficiently in a systematic manner, in trials of limited size but with intensive virological and immunological monitoring and of sufficiently long duration. Only regimens that give the most profound and durable suppression of HIV virus load in such exploratory studies may be taken forward to be studied in large, clinical-end-point trials.

AB HIV causes chronic infection and is associated with persistent viral replication and a high viral **mutation rate.** It is an illusion to think that monotherapy with any antiretroviral agent will have a major and lasting impact on. . . only short duration, and hence it was concluded that drugs should be combined. The response to the limited efficacy of **nucleoside analogue** monotherapy in HIV infection has in many instances been the stance that 'currently available antiretrovirals are no good; it is. . .

=> d hist

(FILE 'HOME' ENTERED AT 16:40:38 ON 06 DEC 2004)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 16:41:15 ON 06 DEC 2004

```
L1        846166 S MUTATE OR MUTATION
L2           158 S NUCLEOBASE ANALOG?
L3         19903 S NUCLEOSIDE ANALOG?
L4         20032 S L2 OR L3
L5         14396 S L1 (A) RATE
L6            27 S L5 (S) L4
L7            13 DUP REM L6 (14 DUPLICATES REMOVED)

=> s l5 (p) l4
L8            44 L5 (P) L4

=> s l8 not l6
L9            17 L8 NOT L6

=> dup rem l9
PROCESSING COMPLETED FOR L9
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L10 8 DUP REM L9 (9 DUPLICATES REMOVED)

=> d ibib abs kwic tot l10

L10 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004567744 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15487935
TITLE: Viral error catastrophe by mutagenic nucleosides.
AUTHOR: Anderson Jon P; Daifuku Richard; Loeb Lawrence A
CORPORATE SOURCE: The Joseph Gottstein Memorial Cancer Research Laboratory, Department of Pathology, University of Washington, Seattle, Washington 98195, USA.. jonand@u.washington.edu
CONTRACT NUMBER: AI42579 (NIAID)
CA102029 (NCI)
CA78883 (NCI)
P30ES07033 (NIEHS)
T32ES0032 (NIEHS)
SOURCE: Annual review of microbiology, (2004) 58 183-205.
Journal code: 0372370. ISSN: 0066-4227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041116
Last Updated on STN: 20041117
AB Riboviruses and retroviruses have the highest rates of mutations of any known organism. Increasing the **mutation rate** of these viruses could exceed the error threshold for viability of a viral population within a host. Recent experiments with mutagenic **nucleoside analogs** validate this new approach to treating infection of RNA viruses. Lethal mutagenesis with HIV-infected cells in culture has been documented and has been postulated to be the mechanism for treatment of hepatitis C with ribavirin. We consider the viral dynamics involved in the formation of a quasispecies, the choice of mutagenic **nucleoside analogs**, and the studies that have demonstrated the feasibility of lethal mutagenesis.
AB Riboviruses and retroviruses have the highest rates of mutations of any known organism. Increasing the **mutation rate** of these viruses could exceed the error threshold for viability of a viral population within a host. Recent experiments with mutagenic **nucleoside analogs** validate this new approach to treating infection of RNA viruses. Lethal mutagenesis with HIV-infected cells in culture has been documented. . . hepatitis C with ribavirin. We consider the viral dynamics involved in the formation of a quasispecies, the choice of mutagenic **nucleoside analogs** , and the studies that have demonstrated the feasibility of lethal mutagenesis.

L10 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:609939 CAPLUS
DOCUMENT NUMBER: 139:146212
TITLE: Screening assay for hepatitis c virus antiviral agents
INVENTOR(S): Schmidt, Emmett Vance; Chung, Raymond Taeyong
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 35 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003148267	A1	20030807	US 2002-292129		20021108
PRIORITY APPLN. INFO.:			US 2001-345405P	P	20011109

AB The invention includes methods of identifying compds. that increase the **mutation rate** of hepatitis C virus. The invention can be used to screen libraries of test compds., including both **nucleoside analogs** and non-**nucleoside analogs.** The methods include: (1) contacting a test cell with a candidate compound, wherein the test cell contains a nucleic acid mol. comprising an infectious hepatitis C viral genome, a ribozyme, and an inducible promoter operably linked to the first and second nucleotide sequences, the ribozyme being configured to remove a 3' sequence unnecessary for replication of the infectious hepatitis C viral genome from a transcript initiated by the inducible promote; and (2) the detection of an increase in hepatitis C virus quasispecies produced by the cell in the presence of the candidate compound Detection of an increase in quasispecies can be accomplished by, e.g., sequencing HCV nucleic acid mols. isolated from the test cell.

AB The invention includes methods of identifying compds. that increase the **mutation rate** of hepatitis C virus. The invention can be used to screen libraries of test compds., including both **nucleoside analogs** and non-**nucleoside analogs.** The methods include: (1) contacting a test cell with a candidate compound, wherein the test cell contains a nucleic acid mol. comprising an infectious hepatitis C viral genome, a ribozyme, and an inducible promoter operably linked to the first and second nucleotide sequences, the ribozyme being configured to remove a 3' sequence unnecessary for replication of the infectious hepatitis C viral genome from a transcript initiated by the inducible promote; and (2) the detection of an increase in hepatitis C virus quasispecies produced by the cell in the presence of the candidate compound Detection of an increase in quasispecies can be accomplished by, e.g., sequencing HCV nucleic acid mols. isolated from the test cell.

L10 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003317744 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12846825
TITLE: Fidelity of hepatitis B virus polymerase.
AUTHOR: Park Sung Gyoo; Kim Younhee; Park Esther; Ryu Hyun Mi; Jung Guhung
CORPORATE SOURCE: School of Biological Science, Seoul National University, Seoul, Korea.
SOURCE: European journal of biochemistry / FEBS, (2003 Jul) 270 (14) 2929-36.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030709
Last Updated on STN: 20030829
Entered Medline: 20030828

AB Although efficient vaccines are available, chronic hepatitis B (HBV) infection poses a major health problem worldwide, and prolonged treatment of chronically infected HBV patients with **nucleoside analogs** often results in drug-resistant HBV variants. Therefore, it is critical to evaluate the contribution of the HBV polymerase to mutations. FLAG-tagged wild-type (FPolE) and mutant (FPolE/D551A) HBV polymerases have been expressed in insect cells and purified. The purified FPolE showed DNA polymerase activity, but FPolE/D551A did not, implying that the activity was derived from FPolE. No 3'-->5'exonuclease activity was detected in FPolE. The fidelity of FPolE was investigated and compared with that of HIV-1 RT, which is highly error-prone. The fidelity of HBV polymerase seems to be achieved by increasing the Km for the dNTP being misinserted. The nucleotide misinsertion efficiency of FPolE and HIV-1 RT ranged from 3.59 x 10-4 (C : T) to 1.51 x 10-3 (G : T) and from 1.75 x 10-4 (C : T) to 1.62 x 10-3 (G : T), respectively, and the

overall misinsertion efficiency of HIV-1 RT was just 1.04-fold higher than that of FPolE, implying that HBV polymerase is fairly error-prone. Though HBV genetic **mutation rate** in replication is thought to be between those in RNA and DNA viruses, our data shows that the rate of mutation by HBV polymerase is higher than the rate of genetic mutation in vivo. This may be a result from more overlapping HBV genes in the HBV genome than that of other retroviruses.

AB . . . chronic hepatitis B (HBV) infection poses a major health problem worldwide, and prolonged treatment of chronically infected HBV patients with **nucleoside analogs** often results in drug-resistant HBV variants. Therefore, it is critical to evaluate the contribution of the HBV polymerase to mutations.. . . HIV-1 RT was just 1.04-fold higher than that of FPolE, implying that HBV polymerase is fairly error-prone. Though HBV genetic **mutation rate** in replication is thought to be between those in RNA and DNA viruses, our data shows that the rate of. . .

L10 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004512639 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15482126
TITLE: Prophylaxis and treatment of hepatitis B recurrence after liver transplantation in the antiviral era.
AUTHOR: Seehofer Daniel; Rayes Nada; Neuhaus Peter
CORPORATE SOURCE: Department of General-, Visceral-, and Transplant Surgery, Charite Campus Virchov, Berlin, Germany.. daniel.seehofer@charite.de
SOURCE: Expert Rev Anti Infect Ther, (2003 Aug) 1 (2) 307-18. Journal code: 101181284. ISSN: 1478-7210.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041015
Last Updated on STN: 20041019

AB Redistribution of virions from extrahepatic reservoirs with resultant reinfection of the graft is a serious complication after liver transplantation for hepatitis B-related liver disease. Prophylaxis of hepatitis B virus recurrence is a major issue in these patients. With the introduction of passive immunoprophylaxis and the development of antiviral drugs, liver transplantation has evolved as an established therapy of hepatitis B-induced end-stage liver failure. However, even under indefinite monoprophylaxis, a significant percentage of patients develop reinfection due to a high **mutation rate** of the hepatitis B virus. Progress, especially in the field of antiviral therapy, has opened new strategies, including combination prophylaxis and therapy, which further improve outcome. On the other hand, the broad use of antiviral drugs brings about new problems such as resistance formation prior to liver transplantation. In addition, due to the high costs of hepatitis B immunoglobulin alternatives such as prophylaxis with **nucleoside analogs** or vaccination are increasingly being investigated.

AB . . . B-induced end-stage liver failure. However, even under indefinite monoprophylaxis, a significant percentage of patients develop reinfection due to a high **mutation rate** of the hepatitis B virus. Progress, especially in the field of antiviral therapy, has opened new strategies, including combination prophylaxis. . . prior to liver transplantation. In addition, due to the high costs of hepatitis B immunoglobulin alternatives such as prophylaxis with **nucleoside analogs** or vaccination are increasingly being investigated.

L10 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002325309 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11948182
TITLE: Substitutions of Phe61 located in the vicinity of template

5'-overhang influence polymerase fidelity and nucleoside analog sensitivity of HIV-1 reverse transcriptase.
AUTHOR: Fisher Timothy S; Prasad Vinayaka R
CORPORATE SOURCE: Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
CONTRACT NUMBER: R01 AI30861 (NIAID)
T32-GM07491 (NIGMS)
SOURCE: Journal of biological chemistry, (2002 Jun 21) 277 (25) 22345-52.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020618
Last Updated on STN: 20030105
Entered Medline: 20020719

AB Human immunodeficiency virus type 1 reverse transcriptase (RT) is an error-prone DNA polymerase. Structural determinants of its fidelity are incompletely understood. RT/template primer contacts have been shown to influence its fidelity and sensitivity to **nucleoside analog** inhibitors. The Phe(61) residue, located within the beta 3 sheet of the finger subdomain, is highly conserved among retroviral RTs. The crystal structure of a ternary complex revealed that Phe(61) contacts the first and second bases of the 5'-template overhang. To determine whether such contacts influence the dNTP-binding pocket, we performed a limited vertical scanning mutagenesis (Phe --> Ala, Leu, Trp, or Tyr) at Phe(61). The F61A mutant displayed the highest increase in fidelity, followed by the F61L and F61W variants, which had intermediate phenotypes. F61Y RT had a minimal effect. The increase in fidelity of the F61A mutant was corroborated by a 12-fold decrease in its forward **mutation rate.** The Phe(61) mutant RTs also displayed large reductions in sensitivity to 2',3'-dideoxythymidine triphosphate and 2',3'-dideoxy,2'3'-didehydrothymidine triphosphate. Mutants displaying the largest increase in fidelity (F61A and F61L) were also the most resistant. These results suggest that contacts between the finger subdomain of human immunodeficiency virus type 1 RT and the template 5'-overhang are important determinants of the geometry of the dNTP-binding pocket.

AB . . . determinants of its fidelity are incompletely understood. RT/template primer contacts have been shown to influence its fidelity and sensitivity to **nucleoside analog** inhibitors. The Phe(61) residue, located within the beta 3 sheet of the finger subdomain, is highly conserved among retroviral RTs.. . . a minimal effect. The increase in fidelity of the F61A mutant was corroborated by a 12-fold decrease in its forward **mutation rate.** The Phe(61) mutant RTs also displayed large reductions in sensitivity to 2',3'-dideoxythymidine triphosphate and 2',3'-dideoxy,2'3'-didehydrothymidine triphosphate. Mutants displaying the largest. . .

L10 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003298485 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12825459
TITLE: Ribavirin: recent insights into antiviral mechanisms of action.
AUTHOR: Reyes G R
CORPORATE SOURCE: Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA.. gregory.reyes@spcorp.com
SOURCE: Current opinion in drug discovery & development, (2001 Sep) 4 (5) 651-6. Ref: 32
Journal code: 100887519. ISSN: 1367-6733.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030627
Last Updated on STN: 20030722
Entered Medline: 20030721

AB Ribavirin, a **nucleoside analog**, used in combination with interferon-alpha (IFN alpha) results in a substantial improvement in the sustained virologic response in chronic hepatitis C. Identified antiviral mechanisms of action for ribavirin include: (i) inhibition of viral encoded polymerases; (ii) inhibition of genomic RNA capping; and (iii) inhibition of cellular encoded enzymes that control de novo synthesis of purine nucleosides. More recently, ribavirin has been shown to engender a bias toward helper T-cell (CD4+) type 1 (Th1) cytokine responses in models of immunity. Recent detailed analysis has also shown that ribavirin can be utilized and incorporated by the polio viral polymerase into genomic and antigenomic transcripts, and is capable of base pairing with either UMP (uridine monophosphate) or CMP (cytidine monophosphate). This results in ribavirin-mediated mutagenesis of the viral genome and has the potential to push the virus beyond tolerable set points in its **mutation rate**, leading to an overall reduced fitness of the viral population. Of the many mechanisms of action demonstrated for ribavirin, the current clinical trials of selective inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitors and immunomodulating agents in hepatitis may facilitate our understanding of what activity (if any) predominates when ribavirin is used in combination with IFN alpha.

AB Ribavirin, a **nucleoside analog**, used in combination with interferon-alpha (IFN alpha) results in a substantial improvement in the sustained virologic response in chronic hepatitis. . . ribavirin-mediated mutagenesis of the viral genome and has the potential to push the virus beyond tolerable set points in its **mutation rate**, leading to an overall reduced fitness of the viral population. Of the many mechanisms of action demonstrated for ribavirin, the. . .

L10 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001220114 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11314862
TITLE: Mitochondrial medicine--molecular pathology of defective oxidative phosphorylation.
AUTHOR: Fosslien E
CORPORATE SOURCE: Department of Pathology, College of Medicine, University of Illinois at Chicago, 60612, USA.. efosslie@uic.edu
SOURCE: Annals of clinical and laboratory science, (2001 Jan) 31 (1) 25-67. Ref: 322
Journal code: 0410247. ISSN: 0091-7370.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Different tissues display distinct sensitivities to defective mitochondrial oxidative phosphorylation (OXPHOS). Tissues highly dependent on oxygen such as the cardiac muscle, skeletal and smooth muscle, the central and peripheral nervous system, the kidney, and the insulin-producing pancreatic beta-cell are especially susceptible to defective OXPHOS. There is evidence that defective OXPHOS plays an important role in atherogenesis, in the pathogenesis of Alzheimer's

disease, Parkinson's disease, diabetes, and aging. Defective OXPHOS may be caused by abnormal mitochondrial biosynthesis due to inherited or acquired mutations in the nuclear (n) or mitochondrial (mt) deoxyribonucleic acid (DNA). For instance, the presence of a mutation of the mtDNA in the pancreatic beta-cell impairs adenosine triphosphate (ATP) generation and insulin synthesis. The nuclear genome controls mitochondrial biosynthesis, but mtDNA has a much higher **mutation rate** than nDNA because it lacks histones and is exposed to the radical oxygen species (ROS) generated by the electron transport chain, and the mtDNA repair system is limited. Defective OXPHOS may be caused by insufficient fuel supply, by defective electron transport chain enzymes (Complexes I - IV), lack of the electron carrier coenzyme Q10, lack of oxygen due to ischemia or anemia; or excessive membrane leakage, resulting in insufficient mitochondrial inner membrane potential for ATP synthesis by the F0F1-ATPase. Human tissues can counteract OXPHOS defects by stimulating mitochondrial biosynthesis; however, above a certain threshold the lack of ATP causes cell death. Many agents affect OXPHOS. Several nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit or uncouple OXPHOS and induce the 'topical' phase of gastrointestinal ulcer formation. Uncoupled mitochondria reduce cell viability. The Helicobacter pylori induces uncoupling. The uncoupling that opens the membrane pores can activate apoptosis. Cholic acid in experimental atherogenic diets inhibits Complex IV, cocaine inhibits Complex I, the poliovirus inhibits Complex II, ceramide inhibits Complex III, azide, cyanide, chloroform, and methamphetamine inhibit Complex IV. Ethanol abuse and antiviral **nucleoside analogue** therapy inhibit mtDNA replication.
By contrast, melatonin stimulates Complexes I and IV and Gingko biloba stimulates Complexes I and III. Oral Q10 supplementation is effective in treating cardiomyopathies and in restoring plasma levels reduced by the statin type of cholesterol-lowering drugs.

AB . . . impairs adenosine triphosphate (ATP) generation and insulin synthesis. The nuclear genome controls mitochondrial biosynthesis, but mtDNA has a much higher **mutation rate** than nDNA because it lacks histones and is exposed to the radical oxygen species (ROS) generated by the electron transport. . . poliovirus inhibits Complex II, ceramide inhibits Complex III, azide, cyanide, chloroform, and methamphetamine inhibit Complex IV. Ethanol abuse and antiviral **nucleoside analogue** therapy inhibit mtDNA replication.
By contrast, melatonin stimulates Complexes I and IV and Gingko biloba stimulates Complexes I and III.. . .

L10 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 95339781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7614900
TITLE: Combination antiretroviral therapy. Back to the future.
AUTHOR: Lange J
CORPORATE SOURCE: Academic Medical Centre, University of Amsterdam, The Netherlands.
SOURCE: Drugs, (1995) 49 Suppl 1 32-7; discussion 38-40. Ref: 33
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19970203
Entered Medline: 19950824

AB HIV causes chronic infection and is associated with persistent viral replication and a high viral **mutation rate.** It is an illusion to think that monotherapy with any antiretroviral agent will have a major and lasting impact on this disease. Monotherapy with antitubercular agents led to dramatic improvements in treatment, but the

development of drug resistance meant that these improvements were of only short duration, and hence it was concluded that drugs should be combined. The response to the limited efficacy of **nucleoside analogue** monotherapy in HIV infection has in many instances been the stance that 'currently available antiretrovirals are no good; it is better not to treat'. In addition, regulatory insistence on clinical end-points has also hampered antiretroviral drug development. It is implied that antiretrovirals must be tested in populations with fairly advanced HIV infection, in whom the least success may be expected. The regulatory bind has also resulted in artificial and counterproductive treatment guidelines. Common sense and experience in infectious diseases dictate that treatment should hit hard and early. No study published thus far undermines the concept that early therapy is better than late therapy or that a tolerable combination of drugs with additive or synergistic anti-HIV activity is better than nucleoside monotherapy. Promising data have been generated in trials on combinations of zidovudine plus didanosine or zalcitabine; a combination of zidovudine and lamivudine (3TC) may be even more promising. (ABSTRACT TRUNCATED AT 250 WORDS)

AB HIV causes chronic infection and is associated with persistent viral replication and a high viral **mutation rate.** It is an illusion to think that monotherapy with any antiretroviral agent will have a major and lasting impact on. . . only short duration, and hence it was concluded that drugs should be combined. The response to the limited efficacy of **nucleoside analogue** monotherapy in HIV infection has in many instances been the stance that 'currently available antiretrovirals are no good; it is. . .

=> d hist

(FILE 'HOME' ENTERED AT 16:40:38 ON 06 DEC 2004)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 16:41:15 ON 06 DEC 2004

```
L1       846166 S MUTATE OR MUTATION
L2          158 S NUCLEOBASE ANALOG?
L3        19903 S NUCLEOSIDE ANALOG?
L4        20032 S L2 OR L3
L5        14396 S L1 (A) RATE
L6           27 S L5 (S) L4
L7           13 DUP REM L6 (14 DUPLICATES REMOVED)
L8           44 S L5 (P) L4
L9           17 S L8 NOT L6
L10           8 DUP REM L9 (9 DUPLICATES REMOVED)
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=> logoff hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.98	41.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.40	-1.40

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 16:43:52 ON 06 DEC 2004